Clinical Conference

Discussant
FAITH T. FITZGERALD, MD

Presented at one of the weekly Grand Rounds, Department of Medicine, San Francisco General Hospital and University of California, San Francisco.

Refer to: Fitzgerald FT: Malaria: A modern dilemma—University of California, San Francisco, and San Francisco General Hospital (Clinical Conference). West J Med 136:220-226, Mar 1982

Malaria: A Modern Dilemma

Malaria remains endemic in large areas of the world, from many of which the United States is receiving more and more immigrants. Because of this, and rapid intercontinental travel, American physicians are likely to again encounter this relatively unfamiliar and potentially rapidly fatal disease. Accurate diagnosis and quick intervention depend upon physician awareness of the pleomorphic clinical manifestations of malaria, its laboratory identification and therapeutic approaches.

MALARIA is the most prevalent of all diseases and a scourge to men and nations throughout history. More than half a century ago Osler recognized that "No infection . . . compares with malaria in the extent of its distribution or its importance as a killing and disabling disease."[1] There are 638 million people who live where malaria is endemic and, in spite of vigorous eradication campaigns and effective prophylactic and therapeutic drugs, more than a million people die each year from this disease. Yet physicians in the United States, a sanitized sanctuary in a world of pandemic disease, often regard malaria as "one of those weird tropical diseases."

Malaria is the commonest acute febrile illness imported into the United States. The recent influx of Asian and Middle Eastern immigrants, and the danger of reestablishing endemic malaria[2] (for the mosquito vector is abundant here), make recognition and understanding of this disease by American physicians imperative. It is noteworthy that the mortality of malaria is higher in civilian victims than among miliary personnel in America. This is attributable to a greater awareness of malaria among military physicians schooled in Vietnam, and reaffirms the point that one cannot diagnose and treat a disease unless one considers it.

Dr. Fitzgerald is Associate Professor, Department of Internal Medicine, and Associate Dean for Student and Curricular Affairs, University of California, Davis, School of Medicine, Davis, California.

Reprint requests to: Faith T. Fitzgerald, MD, Office of the Dean, University of California, Davis, School of Medicine, Davis, CA 95616.

Malarial Species and Cycles

Malaria is transmitted by the bite of the female *Anopheles* mosquito. The injected parasite disappears from the blood of the bitten person, usually within 30 minutes, and invades the parenchymal cells of the liver (primary exoerythrocytic cycle) where it develops for a minimum of six days. Released merozoites then enter erythrocytes and develop there by a process called schizogony. Even with multiple infections (as with multiple mosquito bites at different times) one strain of the parasite becomes dominant, somehow setting the pattern for the others such that the release of parasites from red cells and their entry into other circulating erythrocytes becomes synchronous every 48 to 72 hours. It is with this *breakout* of malarial parasites from erythrocytes that the clinical paroxysm is associated.

Merozoites may also directly reenter liver cells and remain dormant, only to reappear later, causing relapse (secondary exoerythrocytic cycle). *Plasmodium falciparum* is unique in that *all* its merozoites from liver enter erythrocytes. They do not reenter hepatic tissues as do the parasites of other species. Thus it rarely maintains clinical illness greater than one year after infection and true "relapses" do not occur.

Some of the intraerythrocytic parasites develop into the sexual gametocytes which, when taken up by the mosquito during a blood-meal, mate in the insect and complete the cycle.

There are four malarial parasites of clinical importance to man:

- *P falciparum* is the only type that may acutely cause death in the absence of other disease. Falciparum malaria is the form of malaria that represents a medical emergency in the sense of being able to kill within 24 hours of the onset of symptoms, in its association with major complications and in its resistance to chloroquine.
- *P vivax* is the commonest malarial parasite seen in the United States. The clinical manifestations of vivax malaria are generally limited to anemia and episodes of fever.
- *P malariae,* the species causing quartan malaria, is similar in its benignity to *vivax.* However, it is remarkable in its ability to cause relapses long after exposure (perhaps as long as 30 years)[3] and the association it has with the major nonfalciparum malaria complication—the nephrotic syndrome.[4]
- *P ovale* is a West African malarial parasite and is rarely seen in the United States. Clinically, ovale malaria resembles vivax.

Most of the malaria seen in Americans returning from Southeast Asia during the Vietnam War was falciparum or vivax. Because of the shorter incubation period of falciparum (nine days from bite to symptoms, as opposed to two weeks for vivax), and because of the resistance of many strains of *falciparum* to prophylactic drugs, allowing it to become clinically manifest shortly after infection, much of *falciparum*-caused disease is diagnosed in the country of origin. Vivax malaria, on the other hand, may be suppressed by drugs until, on his return home, the traveler stops taking them. Because of this, cases of malaria diagnosed shortly after arrival in the United States may be either falciparum or vivax, whereas most patients whose clinical illness begins several weeks or months after leaving an endemic area have vivax malaria.

A great deal of emphasis has been placed in the past on species-specific diagnosis from blood smears. This is epidemiologically important, but for the clinical situation the crucial difference a physician must know is the distinction between *falciparum* and all others. Whether the parasite is *vivax* or *malariae* is not imminently critical; but one must know if it is *falciparum,* for this is truly a medical emergency. Only falciparum malaria may be acutely fatal.

Many patients will have their clinical courses modified by prophylactic drugs. Diagnosis may be made yet more complex by the fact that all kinds of malaria in the early stages may fail to show the classic asymptomatic periods; that is, synchronization of parasitic cycles may be established only after several days, obscuring the characteristic every third day (tertian) fever of vivax or falciparum malaria, or every fourth day symptoms of malariae (quartan fever). Synchronization may not occur at all during the primary attack, and daily or irregular (and thus clinically unhelpful) fever is especially common in falciparum malaria.

The only sure way of making the diagnosis of malaria and the crucial species differentiation of *falciparum* is by examination of a blood smear. If parasitemia is of a low grade, one must commit oneself to prolonged, careful examination of several blood smears taken at different times. A single negative is insufficient for exclusion of the diagnosis. Parasites may be difficult to identify with certainty on the thin smear (though they can be recognized with experience, even on a standard Wright's stained slide). For the person who sees plasmodiae only occasionally, species identification can be done from the thick smear with greater confidence. The thick smear is but a technique of concentration which involves lysis of red cells with a Giemsa stain fixative.

The smears should be examined with colored plates of typical species forms at one's side. The following generalizations are helpful to keep in mind:

- *Plasmodium vivax* infests principally reticulocytes. Schizont forms are frequent on the smear. Schüffner's dots are present in the red cells.
- *Plasmodium malariae* prefers parasitizing older cells. Like *vivax,* it shows a wide range of morphologically different intraerythrocytic stages of parasite.
- *Plasmodium falciparum,* because it invades red cells of all ages, commonly has the heaviest parasitemia (with the intensity of parasitemia directly correlating with morbidity and mortality). In this species, the examiner seldom sees any intraerythrocytic forms other than rings and gametocytes. Plentiful ameboid trophozoites or schizonts suggest another species. Most character-

istic of *falciparum* are the distinctive large, banana shaped gametocytes.

If one is uncertain of the diagnosis in a patient from Southeast Asia, it is generally wise to assume the worst and treat the patient as though he had falciparum malaria because of the frequency of chloroquine resistance and the rapidity with which severe complications may occur with falciparum.

Clinical Manifestations of Malaria

Classically, all malaria presents as recurrent paroxysms of chills and fever occurring every 36 to 72 hours. The first sign of an attack may be a dull headache or generalized malaise, shortly followed by teeth-rattling chills, cutaneous vasoconstriction and polyuria lasting an hour or less. These chills are most dramatic in *malariae*-caused disease, and may be minimal in falciparum.[5] In the transition from chills to fever, the patient may feel alternately hot and cold, then attain a high fever, with flushing, sustained for two to six hours and terminated by a drenching sweat, leaving the victim exhausted.

The classic features may be altered by the patient's prior experiences with malaria: a partially immune person's symptoms may be far less dramatic, or a first-time victim's experience a sustained or hectic, but noncyclic, fever. Headache, myalgias and a variety of gastrointestinal complaints may accompany the febrile stage of the disease. In addition to the travel history, a clinician should be alerted to the possibility of malaria in the differential diagnosis of an acute febrile illness by the occurrence, on occasion, of high morning fevers[5] and the magnitude of the temperature elevation, frequently as much as 40.6° to 41°C (105° to 106°F)—a level uncommon in other acute febrile illnesses.[6]

Though the clinical presentation of an acute malarial attack may closely resemble endotoxemia (including hypotension in falciparum malaria),[7] there is no evident passively transferrable substance in the blood of the malaria victim (other than the parasites themselves) that will reproduce the clinical syndrome in a recipient. Even the mechanism of the paroxysm, though known to correspond in time with the breakout of parasites from red cells, is unclear.[5,8]

The physical examination in malaria, other than during the paroxysm, is singularly unhelpful. Splenomegaly is variable, perhaps dependent upon the duration of subclinical illness. Only a small percentage of patients will have hepatomegaly. Jaundice is uncommon unless caused by brisk hemolysis. Malignant hyperthermia, with temperatures greater than 41.6° to 42°C (107° to 108°F) is a threat in falciparum, but is fortunately rare.[5] As mentioned, hypotension may occur in falciparum malaria even in the absence of fever, anemia or electrolyte imbalance. Patients may have sustained orthostatic drops in blood pressure that persist as long as two weeks into the recovery phase.[9] Total plasma volume in this condition has been measured and is normal or increased, but effective blood volume is decreased because of vasodilatation and peripheral pooling.[7] The resulting decrease in effective circulating volume may lead to compensatory fluid retention, hyponatremia and, occasionally, generalized edema.[10,11] Adrenocortical function has been studied and is normal.[12]

Complications of Malaria

Major complications of malaria, with one exception, occur exclusively in *falciparum* infections. These severe manifestations occur most frequently when there is a high degree of parasitemia.

Cerebral malaria occurs in about 2 percent of patients with acute falciparum malaria.[13] It may be manifested by changes in consciousness ranging from confusion to coma, behavioral changes, increased muscle tone, seizures, movement disorders, focal neurologic signs or transient cerebellar dysfunction.[13,14] The pathophysiology of cerebral malaria is unclear, but it has been attributed to intravascular coagulation of the blood supply of brain,[15] immune vasculomyelinopathy in which *Plasmodium falciparum* is the antigen,[16] increased "stickiness" of parasitized red cells with consequent vascular occlusion, or capillary leak with cerebral edema and sludging of blood flow which, combined with anemia, leads to cerebral anoxia.[13,17] Cerebral malaria is the most fearsome of all complications of this disease, and is present in a large number of those dying with falciparum infections.[18]

Pulmonary manifestations of falciparum malaria, either noncardiogenic pulmonary edema or severe intraalveolar hemorrhage, may dominate the clinical features. One of ten patients with ordinary malarial infections may have respiratory symptoms—a cough, for example. In a few patients sudden and severe pulmonary edema will develop several days after the initiation of therapy.[19] Since this commonly occurs concurrently with cerebral malaria, a neurogenic cause may be operative. Other possibilities include increased capillary permeability, sludging of parasitized erythrocytes with capillary occlusion or consumption coagulopathy.[19,20] Progressive, refractory hypoxemia, diffuse infiltrates on x-ray films of the chest and pathologic findings of pulmonary edema, scattered hemorrhage and alveolar septal thickening make this complication most resemble an adult respiratory distress syndrome, or shock lung.[18]

Acute renal failure is one of the commonest major complications of falciparum malaria. *Blackwater* fever describes a massive, severe hemoglobinuria from abrupt hemolysis. Though it may be associated with acute renal shutdown, this hemoglobinuria need not necessarily impair renal function.[21] Formerly thought to be related to antimalarial therapy, several cases of blackwater fever have been documented in untreated patients.[22,23] And renal failure may clearly occur in the absence of blackwater fever.[24] Renal compromise may range from proteinuria[25] to oliguric acute renal failure.[26] The pathogenesis of the renal failure is probably similar to that of the acute tubular necrosis of other major medical and surgical stresses,[26,27] though intravascular coagulation has also been held responsible.[15] Predisposing features to renal shutdown appear to be severe hemolysis, intense parasitemia, and delay in adequate diagnosis and antimalarial therapy.[28] Early dialysis is generally required because of the severe catabolic state of many of these patients.[21]

The single major nonfalciparum complication of malaria also involves the kidneys, and is the nephrotic syndrome which occurs in chronic *Plasmodium malariae* infections.[4] On biopsy, histopathologic changes have ranged from diffuse or focal glomerulonephritis to patchy membranous change.[8] Immunocomplex disease, with *Plasmodium malariae* as the antigen, is probable.

The liver is almost universally involved in malaria. Even in *falciparum* infections, in which there is no secondary extraerythrocytic sequestration of the merozoites in hepatocytes, liver enzymes may be elevated and histologic abnormalities present on biopsy include Kupffer cell hyperplasia and pigmentation and periportal mononuclear cell infiltrates.[29] Malarial hepatitis is for the most part clinically inconsequential, however, and jaundice if it occurs is predominantly hemolytic.

Diarrhea may occur as part of the malarial attack, but intestinal functional abnormalities are more frequently subclinical. Studies in falciparum malaria have shown intestinal malabsorption with small bowel edema and vascular congestion.[30]

Spontaneous rupture of a chronically enlarged spleen is very rare. Though uncommon, spontaneous splenic rupture in a primary attack of acute malaria may be life-threatening.[3,31]

The Hematologic Sequelae of Malaria

Hemolysis characterizes all types of malaria, but because *vivax* prefers young erythrocytes and *malariae* old ones, only falciparum malaria—with its nondiscriminative parasitization of red cells of any age—has been associated with massive hemolysis. Anemia is not a constant finding in malaria, but is directly related to the intensity of the parasitemia. Yet the precise mechanism of anemia in malaria is a mystery. It is easy to conceive as a simple mechanical disruption of red cells by the parasites, yet both parasitized and unparasitized cells are destroyed at an accelerated rate, and uninfected as well as parasitized red cells are removed from circulation by the reticuloendothelial system.[21] Phagocytosis of erythrocytes by the reticuloendothelial system rather than mechanical intravascular hemolysis may be a major factor in the anemia of malaria.

Both parasitized and unparasitized cells in infected patients show increased osmotic fragility[32] and abnormalities of intraerythrocytic sodium and potassium concentrations suggest that red cells from infected animals may have an altered cation permeability that predisposes to their destruction.[33,34] One set of labeling experiments suggests that the spleen may actually remove parasites from infected red cells and then return these damaged but unparasitized cells to the circulation.[35] These altered cells may be the "unparasitized" cells in which abnormalities are found, and this concept would provide an explanation for the adverse effect of splenectomy in malaria as well as for the presence of spherocytes in malarious animals with intact spleens.

It has also been proposed that the metabolic demands of intraerythrocytic parasites may, by causing changes in membrane and in sodium-potassium balance, decrease the red cells' capacity to maintain normal surface negative charge. This would lead to increased aggregation and sludging of red cells in the microcirculation, accounting for the vaso-occlusive complications of the heavily parasitized host.[35]

Occasional Coombs' positivity in patients with malaria[36] has led to the speculation that autoimmunity plays a role in hemolysis.[37]

Marrow production of erythrocytes is also impaired in malaria. Ferrokinetic studies and examination of bone marrow in victims of malaria suggest two mechanisms—one in acute and one in more chronic malaria. During an acute primary parasitemia there is a general depression of erythropoiesis. In chronic malaria, however, there may be an increase in erythroid elements in marrow, suggesting either a retardation of red cell maturation or impaired release.[38]

All these changes are quite independent of the hemolytic responses to certain antimalarials in glucose-6-phosphate dehydrogenase deficient persons.

Thrombocytopenia is common in malaria.[21] In conjunction with depletion of a broad spectrum of coagulation factors, it has been attributed by some investigators to a disseminated intravascular coagulation in falciparum malaria.[39] Others have argued persuasively for an immune-mediated thrombocytopenia.[21]

Diagnosis of Malaria

The diagnosis of malaria should be considered in any febrile patient who has been in or through an endemic area. Most contemporary victims are infected in Africa, Central and South America, India, Haiti, the Dominican Republic and Southeast Asia.[40] Others at risk include drug addicts,[41] in whom modified symptoms of malaria—chills, tremulousness, fevers, aches and pains—may be interpreted as drug withdrawal. In this case, the parasite is transmitted by shared needles. The transmission of malaria by transfusions of blood is well documented.[42,43] Transfusion-induced malaria may present with a prolonged incubation phase and atypical symptoms. The donor of the infected blood may be totally asymptomatic and surprisingly removed in time from the period of last exposure.[44] Even with modern component transfusions, malaria remains a risk; it has been reported to complicate leukocyte transfusion.[45] Malarial parasites have been described within human platelets,[46] suggesting yet another possible source of accidental infection.

Since needle or transfusion malaria transmits no hepatic merozoites, there is no exoerythrocytic phase to the illness. This makes for shorter courses of disease than in naturally acquired infections and for a different therapeutic approach.

The diagnosis of malaria is best proved by showing the presence of the parasite in the blood. Plasmodia are most readily found in capillary blood obtained by finger stick. There is no reason to await the fever spike before seeking the parasite; with falciparum malaria, in fact, parasitemia is heaviest during the afebrile periods.[5] Demonstration of the parasites may require diligent and repeated searches, and occasionally bone marrow aspiration.[47] Immunologic diagnostic techniques include indirect hemagglutination, direct immunofluorescence[48] and microhemagglutination tests.[49] These tests appear to be more useful for epidemiologic and historical surveys than for diagnosis in acutely ill patients. There is evidence that this antibody response plays a protective role in malaria,[21] giving a relative resistance to reinfection. Malaria hyperimmune globulin lowered parasitemia when given to children infected with *Plasmodium falciparum*.[50] Adults who live in areas endemic for malaria commonly have pronounced hypergammaglobulinemia which decreases when the persons are adequately treated for malaria.[50] Yet only a small amount of the total quantity of the immunoglobulin elevation in malaria seems to represent specific antibody against the parasite, and the function of most of the immunoglobulin remains obscure.[21]

Therapy of Malaria

Antimalarial drugs fall pharmacologically into four major categories[51]:

- *The quinolone derivatives,* such as quinine and chloroquine, interfere with nucleic acid replication and glucose metabolism.
- *The aminobenzoic acid (PABA) antagonists,* such as sulfonamides and dapsone, take advantage of the parasite's requirement for neosynthesis of folic acid by interfering with that synthesis.
- *Folic acid reductase inhibitors,* such as pyrimethamine and trimethoprim, work like the PABA antagonists but interfere at a different point of the folic acid synthetic pathway.
- *Other agents* are used, such as colchicine and tetracycline. First used as an antimalarial in World War II, colchicine decreases the tendency for falciparum malaria to recrudesce after quinine therapy.[52] Tetracycline, in combination with quinine, has also been used with some success in the treatment of chloroquine-resistant falciparum malaria.[53]

There are two types of cure in malaria therapy: *clinical cure* is the termination of the acute attack; *radical cure* is the eradication of the infection itself. Clinical cure requires the use of a drug effective against circulating blood forms. Most effective for this, for all sensitive strains, is chloroquine. This agent also produces radical cure in chloroquine-sensitive falciparum malaria (which has no secondary exoerythrocytic sequestration in liver) and in transfusion or needle malaria which—no matter what the malarial species—also lacks hepatic parasites. In other types of malaria, one requires chloroquine plus a drug effective against the liver phase of the parasite. The drug of choice for this is primaquine.

Because of the high incidence of chloroquine resistance among *falciparum* from Vietnam, quinine is generally the drug of choice with this species. With severe falciparum malaria, or in any major complication of this malignant infection, parenteral administration of quinine is preferred, with transfer to orally given medication on clinical improvement. In order to prevent relapse, quinine therapy of falciparum malaria should be accompanied by therapy with pyrimethamine and a sulfa drug. Steroid therapy has been recommended as an adjunct to the specific antimalarials in cerebral malaria[13,54] and falciparum pulmonary edema.[21] Heparin therapy has been suggested to benefit patients with falciparum malaria in whom disseminated intravascular coagulation seems to be playing a role in major complications.[15,26,35] Others urge great caution in the use of anticoagulants, however.[21]

Therapies are outlined in Table 1.

Persons planning a visit to endemic malarious areas in which there are no known chloroquine-resistant strains should take 300 mg of chloroquine base weekly, beginning one or two weeks before entry to the infested region and continuing for eight weeks after return to the United States. Those who cannot avoid passing through nations in which chloroquine-resistant falciparum occurs are best advised to consult the Centers for Disease Control, Atlanta, for the most recent prophylactic recommendations. Some of those formerly used are now ineffective or (as with dapsone) shown to be potentially extremely toxic, even fatal.[55]

Conclusions

Whether malaria can be eliminated as a world disease remains to be seen. We remain obliged to continue trying, however, in this ancient battle, to develop and perpetuate mosquito elimination campaigns; to develop effective, nontoxic therapeutic agents more quickly than the parasite can develop resistance, and to remain perpetually aware, in our care of the individual febrile patient, of the possibility of this diagnosis.

REFERENCES

1. Osler W: Malaria, *In* Christian HA (Ed): Osler's Principles and Practice of Medicine, 13th Ed. New York, D. Appleton-Century Co, 1938, pp 381-394

TABLE 1.—*The Therapy of Malaria*

Species	*Therapy*	
Plasmodium falciparum (unknown sensitivity or known chloroquine resistant)	In most cases:	
	Quinine sulfate	650 mg given orally three times a day for 14 days plus
	Pyrimethamine	25 mg given orally two times a day for 3 days plus
	Sulfonamide	2 grams initially, then
		500 mg given orally every 6 hours for 5 days
	In life threatening cases (cerebral malaria, pulmonary edema, malignant hyperthermia, etc):	
	Quinine dihydrochloride	600 mg in 600 ml of normal saline solution very slowly intravenously every 8 hours
		Switch to the oral regimen outlined above *as soon as possible.*
Plasmodium vivax *Plasmodium malariae* *Plasmodium ovale*	Chloroquine base	600 mg orally immediately, after 6 hours
		300 mg orally, then
		300 mg orally daily for 2 days then
	Primaquine base	15 mg orally daily for 14 days
Plasmodium falciparum (known chloroquine sensitive) Transfusion, needle malaria (any species)	Chloroquine base	600 mg orally immediately, after 6 hours 300 mg orally, then 300 mg orally daily for 2 days

2. Stirling EL, Rowsell T: Malaria in California (Correspondence). West J Med 1981 Jun; 134:545

3. Wilcocks C, Manson-Bahr PEC: Malaria, chap 4, Manson's Tropical Diseases, 17th Ed. Baltimore, Williams & Wilkins Co, 1972, pp 39-86

4. Hendrickse RG, Glasgow EF, Adeniyi A, et al: Quartan malarial nephrotic syndrome. Lancet 1972 May 27; 1:1143-1148

5. Barrett-Connor E: Malaria. Calif Med 1971 Aug; 115:19-24

6. Deller JJ: Malaria—Again a diagnostic consideration. J Acad Fam Prac 1972 Feb; 5:68-73

7. Sonnenwirth AC, Keating JP, Waltman S: Malaria (1969). JAMA 1969 Aug 4; 209:687-692

8. Neva FA: Malaria—Recent progress and problems. N Engl J Med 1967 Dec 7; 277:1241-1252

9. Blount RE Jr: Acute falciparum malaria. Ann Intern Med 1969 Jan; 70:142-147

10. Brooks MH, Malloy JP, Bartelloni PJ, et al: Pathophysiology of acute falciparum malaria: I. Correlation of clinical and biochemical abnormalities. Am J Med 1967 Nov; 43:735-744

11. Malloy JP, Brooks MH, Barry KG: Pathophysiology of acute falciparum malaria: II. Fluid compartmentalization. Am J Med 1967 Nov; 43:745-750

12. Brooks MH, Barry KG, Cirksena WJ, et al: Pituitary-adrenal function in acute falciparum malaria. Am J Trop Med Hyg 1969 Nov; 18:872-877

13. Daroff RB, Deller JJ, Kash AJ, et al: Cerebral malaria. JAMA 1967 Nov 20; 202:679-682

14. Chipman M, Cadigan FC, Benjapongse W: Involvement of the nervous system in malaria in Thailand. Trop Geogr Med 1967; 19:8-14

15. Jaroonvesama N: Intravascular coagulation in falciparum malaria. Lancet 1972 Jan 29; 1:221-223

16. Toro G, Roman G: Cerebral malaria. Arch Neurol 1978 May; 35:271-275

17. Maegraith B: Complications of falciparum malaria. Bull NY Acad Med 1969 Oct; 45:1061-1064

18. Heineman HS: The clinical syndrome of malaria in the United States. Arch Intern Med 1972 Apr; 129:607-616

19. Brooks MH, Kiel FK, Sheehy TW, et al: Acute pulmonary edema in falciparum malaria. N Engl J Med 1968 Oct 3; 279: 732-737

20. Fletcher JR, Butler T, Kopriva CJ, et al: Acute *Plasmodium falciparum* malaria. Arch Intern Med 1972 Apr; 129:617-619

21. Neva FA, Sheagren JN, Shulman NR, et al: Malaria: Host-defense mechanisms and complications. Ann Intern Med 1970 Aug; 73:295-306

22. Inman M, Hano J, Gilliland P, et al: The clinical spectrum of blackwater fever. Clin Res 1967 Apr; 15:307

23. Dukes DC, Sealey BJ, Forbes JI: Oliguric renal failure in blackwater fever. Am J Med 1968 Dec; 45:899-903

24. Sheehy TW, Reba RC: Complications of falciparum malaria and their treatment. Ann Intern Med 1967 Apr; 66:807-809

25. Berger M, Birch LM, Conte NF: The nephrotic syndrome secondary to acute glomerulonephritis during falciparum malaria. Ann Intern Med 1967 Dec; 67:1163-1171

26. Stone WJ, Hanchett JE, Knepshield JH: Acute renal insufficiency due to falciparum malaria. Arch Intern Med 1972 Apr; 129:620-628

27. Maegraith BG, Findlay GM: Oliguria in blackwater fever. Lancet 1944 Sep 23; 2:403-404

28. Sheehy TW: Disseminated intravascular coagulation and severe falciparum malaria. Lancet 1975 Mar 1; 1:516

29. Deller JJ Jr, Cifarelli PS, Berque S, et al: Malaria hepatitis. Milit Med 1967 Aug; 132:614-620

30. Olsson RA, Johnston EH: Histopathologic changes and small bowel absorption in falciparum malaria. Am J Trop Med Hyg 1969 May; 18:355-359

31. DeSaram GSW, Townsend RF: Spontaneous rupture of the spleen in malignant tertian malaria. Lancet 1943 May 8; 1:584-585

32. George JN, Wicker DJ, Fogel BJ, et al: Erythrocyte abnormalities in experimental malaria. Proc Soc Exper Biol Med 1967 Apr; 124:1086-1090

33. Overman RR: Reversible cellular permeability alterations in disease—In vivo studies on sodium, potassium and chloride concentrations in erythrocytes of the malarious monkey. Am J Physiol 1948 Jan; 152:113-121

34. Dunn MJ: Alterations of red cell sodium transport during malarial infection. J Clin Invest 1969 Apr; 48:674-684

35. Conrad ME: Pathophysiology of malaria—Hematologic observations in human and animal studies. Ann Intern Med 1969 Jan; 70:134-141

36. Adner MM, Alstatt LB, Conrad ME: Coombs'-positive hemolytic disease in malaria. Ann Intern Med 1968 Jan; 68:33-38

37. Zuckerman A: Recent studies on factors involved in malarial anemia. Milit Med 1966 Sep; 131(Suppl):1201-1216

38. Srichaikul T, Makumkrong W, Poshyachinda V, et al: Ferrokinetic studies and erythropoiesis in malaria. Arch Intern Med 1969 Nov; 124:623-628

39. Dennis LH, Eichelberger JW, Inman MM, et al: Depletion of coagulation factors in drug-resistant *Plasmodium* falciparum malaria. Blood 1967 May; 29:713-721

40. Butler T, Warren KS, Mahmoud AAF: Algorithms in the diagnosis and management of exotic diseases—XIII. Malaria. J Infect Dis 1976 Jun; 133:721-726

41. Saylor LF: Induced vivax malaria among users of intravenous heroin. Calif Med 1971 Jun; 114:73-75

42. Brooks MH, Barry KG: Fatal transfusion malaria. Blood 1969 Dec; 34:806-810

43. Czapek EE, Barry DW, Gryboski JD: Malaria in an infant transmitted by transfusion. JAMA 1968 May 6; 204:549-550

44. Verdrager J: Cerebral malaria following blood transfusion. J Trop Med Hyg 1969 Jun; 72:131-133

45. Dover AS, Guinee VF: Malaria transmission by leukocyte component therapy. JAMA 1971 Sep 20; 217:1701-1702

46. Fajardo LF, Tallent C: Malarial parasites within human platelets. JAMA 1974 Aug 26; 229:1205-1207

47. Chojnacki RE, Brazinsky JH, Barrett ON Jr: Transfusion-induced falciparum malaria. N Engl J Med 1968 Oct 31; 279:984-985

48. Kagan IG, Mathews H, Sulzer AJ: The serology of malaria: Recent applications. Bull NY Acad Med 1969 Oct; 45:1027-1042

49. Rogers WA Jr, Fried JA, Kagan IG: A modified indirect microhemagglutination test for malaria. Am J Trop Med Hyg 1968 Nov; 17:804-809

50. Cohen S, McGregor IA, Carrington S: Gamma globulin and acquired immunity to human malaria. Nature (London) 1961 Nov 25; 192:733-737

51. Hunsicker LG: The pharmacology of the antimalarials. Arch Intern Med 1969 Jun; 123:645-649

52. Reba RC, Sheehy TW: Colchicine-quinine therapy for acute falciparum malaria acquired in Vietnam. JAMA 1967 Aug 14; 201:553-554

53. Colwell EJ, Hickman RL, Kosakal S: Tetracycline treatment of chloroquine-resistant falciparum malaria in Thailand. JAMA 1972 May 1; 220:684-686

54. Woodruff AW, Dickinson CJ: Use of dexamethasone in cerebral malaria. Br Med J 1968 Jul 6; 3:31-32

55. Barrett-Connor E: Chemoprophylaxis of malaria for travelers. Ann Intern Med 1974 Aug; 81:219-224